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16. ABSTRACT

In the intraperitoneal study, test groups of male and female Sprague-Dawley rats were given daily doses of 0,1.7 or 3.0 mg/kg of rotenone for 42 days. The high rotenone dosage groups showed decrease in weight gain but there was no effect on mortality. There were numerous mammary gland neoplasms, mostly fibroadenomas, detected but they occurred with similar frequency among control and treatment groups. Except for two lymphosarcomas which occurred in high dose females, all other neoplasms were rare and/or not dosage related.

In the oral study, groups of male and female Wistar rats were given daily doses of 0, 1.7 or 3.0 mg/kg of rotenone by gavage for 42 days. There were no appreciable effects of rotenone dosage on body weigh, mortality, or non-neoplastic disease. Ductal ectasias and cysts were slightly more prevalent in mammary glands of dosed females as compared to controls.

There was no evidence from either the intraperitoneal or oral project that rotenone induced mammary neoplasia in the rat strains studied. The significance of the slight increases in fibrosarcomas and fibromas in both the intraperitoneal and oral studies and in adrenal cortical adeomas in the oral study was inconclusive.

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CARCINOGENIC POTENTIAL OF ROTENONE

PHASE II: ORAL AND INTRAPERITONEAL ADMINISTRATION TO RATS

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FOREWORD

The many benefits of our modern, developing, industrial society are accompanied by certain hazards. Careful assessment of the relative risk of existing and new man-made environmental hazards is necessary for the establishment of sound regulatory policy. These regulations serve to enhance the quality of our environment in order to promote the public health and welfare and the productive capacity of our Nation's population.

The Health Effects Research Laboratory, Research Triangle Park, conducts a coordinated environmental health research program in toxicology, epidemiology, and clinical studies using human volunteer subjects. These studies address problems in air pollution, non-ionizing radiation, environmental carcinogenesis and the toxicology of pesticides as well as other chemical pollutants. The Laboratory participates in the development and revision of air quality criteria documents on pollutants for which national ambient air quality standards exist or are proposed, provides the data for registration of new pesticides or proposed suspension of those already in use, conducts research on hazardous and toxic materials, and is primarily responsible for providing the health basis for non-ionizing radiation standards. Direct support to the regulatory function of the Agency is provided in the form of expert testimony and preparation of affidavits as well as expert advice to the Administrator to assure the adequacy of health care and surveillance of persons having suffered imminent and substantial endangerment of their health.

Rotenone, the extract of derris root, has long been used as an insecticide and fish poison. A recent report by the Spanish investigators Gosalvez and Merchan has shown rotenone to produce mammary tumors in rats by intraperitoneal or dietary dosage. The present study was carried out to determine the possible carcinogenic effect of rotenone in two different rat strains.

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Director
Health Effects Research Laboratory

Abstract

A published report has described mammary tumors in rats dosed with rotenone either intraperitoneally or in the diet. The present study was carried out to determine the possible carcinogenic effect of the compound in two different rat strains.

In the intraperitoneal study, test groups of male and female Sprague-Dawley rats were given daily doses of 0, 1.7 or 3.0 mg/kg of rotenone for 42 days. The animals were observed for an additional 18 months until death or sacrifice. The high rotenone dosage groups showed some decrease in weight gain but there was no effect on mortality. The only non-neoplastic lesions which occurred with substantially greater frequency in rotenone-treated animals as compared to controls included myocardial fibrosis and/or lymphoreticular myocarditis in both high and low dosage groups of both sexes and cystic ductular dilatations in mammary glands of the female high dosage group. There were numerous mammary gland neoplasms, mostly fibroadenomas, detected but they occurred with similar frequency among control and treatment groups. Except for two lymphosarcomas which occurred in high dose females, all other neoplasms were rare and/or not dosage related.

In the oral study, groups of male and female Wistar rats were given daily doses of 0, 1.7 or 3.0 mg/kg of rotenone by gavage for 42 days. The rats were observed for an additional 12 months until death or sacrifice. There were no appreciable effects of rotenone dosage on body weight, mortality, or non-neoplastic disease. Neoplasms were observed in mammary glands of three female rats. Multiple adenomas were present in two animals, one from the control group and one from the low dosage group. A small, early carcinoma and an adenocarcinoma were present in one animal in the low dosage group. Ductal ectasias and cysts were slightly more prevalent in mammary glands of dosed females as compared to controls. Adrenal cortical adenomas occurred in slightly greater frequency in dosed than in control animals. Fibrosarcomas occurred in subcutaneous sites in three males from the high dosage group and one fibroma was observed in a male rat from the low dosage group.

There was no evidence from either the intraperitoneal or oral project that rotenone induced mammary neoplasia in the rat strains studied. The significance of the slight increases in fibrosarcomas and fibromas in both the intraperitoneal and oral studies and in adrenal cortical adenomas in the oral study was inconclusive.

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INTRODUCTION

In a brief communication published in 1973 (Cancer Research 33:3047), Gosalvez and Merchan described experiments in which mammary tumors were found in rats which were fed rotenone. In these studies, 4 series of female albino rats of a strain which reportedly has a natural mammary tumor incidence of 0.5 tumors per 1000 rats per year, were given intraperitoneal injections of rotenone (K & K Laboratories, Inc., Plainview, N.Y., 1.7 mg/kg body weight) dissolved in 0.1 ml sunflower oil on 42 consecutive days. Control animals received 0.1 ml of vehicle. At study initiation the rats were 35 days old (approximately 100 grams each), and were observed for up to 19 months after treatment. In the first series, 8 out of 8 rats exhibited mammary tumors between months 6 and 11 after treatment while 10 controls had no tumors after 19 months. Several of these tumors were histologically diagnosed as "adenomas with accentuated interstitial fibrosis and showed localized areas with adenocarcinomatous transformation: 1 was diagnosed as a differentiated adenocarcinoma. All tumors were encapsulated and did not show metastasis." Four to five successful tumor transplants out of 30 trials were made to normal rats. Primary and transplanted tumors developed slowly, requiring 7 to 12 months after initial detection before full development was achieved.

In order to further evaluate the carcinogenic potential of rotenone in rats, and in attempt to confirm the findings of Gosalvez and Merchan, long term studies were performed in Sprague-Dawley and Wistar rats treated by intraperitoneal injection or oral gavage.

Studies included in this report and inclusive performance dates are shown below:

Title and Description	Receipt of Test Animals	Dose Initiation	Final Sacrifice of Animals
(1) Fourteen-Day Feed Palatability Study	1/7/76	1/14/76	2/4/76
(2) Eighteen-Month Carcinogenicity Study Rotenone Administered Intraperitoneally for 42 Days, Followed by 17-Month Observation Period	1/27/76	2/9/76	8/23/77
(3) Fourteen-Month Carcinogenicity Study Rotenone Administered by Oral Gavage for 42 Days, Followed by 12-Month Observation Period	6/8/76 and 6/15/76	7/6/76	8/25/77

OBJECTIVES, METHODS, AND OBSERVATIONS

Rotenone Chemistry and Handling

The rotenone for all phases of these studies was obtained from S. S. Penick and Company. The material was reported by the supplier to be 98+ percent pure with traces of other rotenoids. High pressure liquid chromatographic (HPLC) analyses performed at Battelle according to a published procedure (J. Chromatography 134:207, 1977), demonstrated the chemical to be 95+ percent pure. The chemical was stored in desiccators under nitrogen at -20°C until used.

Rotenone was prepared for oral gavage by adding appropriate amounts of the chemical to corn oil, followed by stirring the mixture to suspend the chemical. Corn oil (Mazola) was purchased from a local grocery store. Fresh gavage suspensions were prepared daily. In the rotenone palatability study, a suspension of rotenone in corn oil was poured onto the surface of pre-weighed amounts of Purina Rat Chow Meal in a twin shell blender, and mixed for 30 minutes. Previous feed analyses by HPLC indicated that rotenone degraded very rapidly following its addition to feed, with a half-life of less than 2 days.

However, when rotenone was suspended in corn oil, and then added to feed in a final corn oil concentration of 1 percent, 92 percent of the rotenone could be recovered after one week. Subsequently, all rotenone diets were made weekly and included 1 percent corn oil for stability.

Animal Care and Handling

Rats were housed in polycarbonate cages which measured 19.0 x 10.5 x 6.2 inches. Water and Purina Rat Chow were provided ad libitum throughout all studies. Environmental conditions included relative humidity - 45 to 55 percent, temperature - 71 to 73°F, and 12 hours light - 12 hours dark lighting cycles. Cage bedding was changed once per week when rats were singly housed, twice weekly for multiple-housed rats. Rats were identified by a toe clipping-ear punching scheme as illustrated in Figure 1.

Pathology

Necropsies were performed on animals which died spontaneously and those which were terminated at the end of the exposure period. Necropsies were performed by technicians skilled in rodent necropsy techniques with a supervising pathologist present for interpretation and recording of lesions. Tissues were placed in 10-percent neutral buffered formalin for fixation prior to processing and slide preparation. Processing was conducted in the usual manner and slides were stained with hematoxylin and eosin as described in the BCL Manual on Histopathology Procedures.

The following tissues were preserved for microscopic examination:

Abdominal skin	Eye	Seminal Vesicle	Pancreas
Mammary Gland	Bone Marrow	Salivary Gland	Liver
Trachea	Tonsil	Esophagus	Thyroid
Lung	Kidney	Stomach	Parathyroid
Heart	Urinary Bladder	Duodenum	Adrenal
Bronchial L.N.	Ovary	Jejunum	Rib & Femur
Mandibular L.N.	Uterus	Ileum	Brain
Mesenteric L.N.	Testicle	Cecum	Spinal Cord
Spleen	Epididymis	Colon	Sciatic Nerve
Thymus	Prostrate	Muscle	

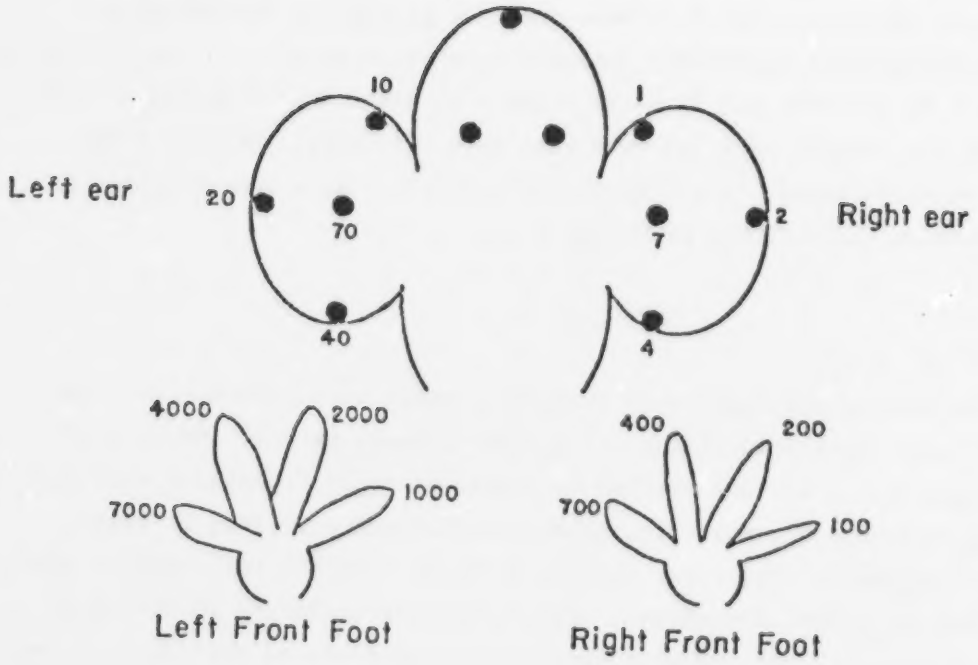

FIGURE 1. RODENT NUMBERING SYSTEM

Weights for the following organs were obtained at necropsy: heart, pituitary, adrenal and thyroid glands, brain, testicles, ovaries, spleen, liver, and kidneys.

Microscopic examination of tissues from these animals were performed by board certified or board eligible pathologists. Tissues from the groups of rats treated via intraperitoneal injection were evaluated by Drs. Steve Weisbrode and Edward Hoover, Veterinary Pathology Consultants, 1925 Coffey Road, Columbus, Ohio 43210.

Data and Test Materials Storage

All records, tissues, paraffin blocks, microscopic slides, and reports for this study will be stored in Battelle's archives.

Palatability Study

The following study was performed to test the palatability of 500 and 1000 ppm rotenone diets in rats,and was conducted as a preliminary task leading to the verification of work performed at other laboratories.

Methods

Twenty Sprague-Dawley derived rats were obtained from Laboratory Supply Company. Body weights ranged from 125 to 145 grams (females) and 150 to 175 grams (males) on Day 0 of the dosed feeding period. Rats were individually housed, and quarantined for 7 days prior to exposure to rotenone.

Five rats of each sex were assigned to 1 of 2 dosage groups. Dosed feeds were prepared which contained either 500 or 1000 ppm rotenone and 1 percent corn oil. These feeds were presented to the rats for 2 weeks, followed by 1 week exposure of the rats to control feed (no corn oil). Individual rats and feed remaining in feed pans were weighed weekly to obtain body weight and feed consumption values.

Observations

The mean body weights and feed consumption data are presented in Figure 2. Mean body weight gains were suppressed in females fed either 500 or 1000 ppm rotenone in the diet. Females appeared to be more sensitive to the chemical than male rats in this respect. Male rats experienced smaller weight gains when fed 1000 ppm rotenone as opposed to 500 ppm diets.

Feed consumption was slightly higher for rats fed 500 ppm rotenone as compared to those fed 1000 ppm (Days 7-14). When rats were returned to normal diets (Days 14-21), feed consumption increased by a factor of 2. It is concluded that feed containing rotenone at a concentration as low as 500 ppm is less palatable to rats than normal feed, and that its ingestion at this concentration leads to depressed body weight gains in immature rats.

Eighteen-Month Carcinogenesis Study

The intent of this phase of the project was to duplicate, in a different strain of rats, the earlier study carried out by Gosalves and Merchan (see INTRODUCTION) in which mammary tumors were found in rats following intraperitoneal administration of rotenone.

Methods

One hundred and thirty Sprague-Dawley rats were obtained from the Charles River Company, 65 of each sex. Body weights on the first day of dosing were 67 to 156 grams for females, and 110 to 169 grams for males. Rats were housed in groups of 2 rats per cage. Rats were held in-house for quarantine for 13 days prior to dose initiation.

Following quarantine, the rats were assigned to one of 3 treatment groups. Rotenone was prepared for injections by pre-weighing amounts of the chemical which were determined to be appropriate for the following week. These amounts were calculated from the mean weights of the rats in a specific group using the previous week's body weights, and the estimated weight increase for the following week, using supplier's growth-rate data. All samples were suspended in corn oil on the day of dosing and administered by intraperitoneal injection in a volume of 0.1 ml. Test groups, 25 males and 25 females each, received doses of 1.7 or 3.0 mg of rotenone per kilogram body weight. Control rats, 15

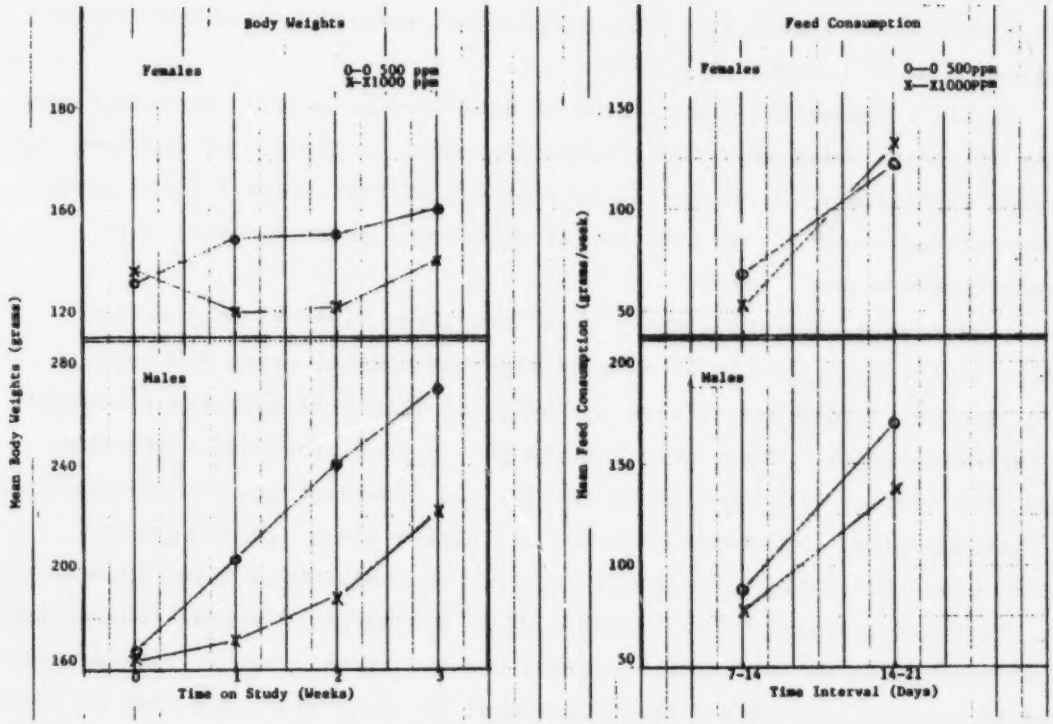

FIGURE 2. MEAN BODY WEIGHTS AND FEED CONSUMPTION DATA — ROTENONE PALATABILITY FEEDING STUDY

male and 15 female, received 0.1 ml corn oil injections. Injections were made on 42 consecutive days. Following the dosing period, the rats were observed for a period of 17 months at which time the surviving animals were necropsied.

Observations

The mean body weight data are presented in Figure 3. Male rats which received 3.0 mg/kg rotenone exhibited up to 25 percent lower body weights than controls during the 18-month study, while the 1.7 mg/kg group maintained body weights intermediate to those of controls and the high dose animals. The high dose-treated female rats also experienced reduced body weights which were no less than 87 percent of controls.

Table 1 presents the rat survival data for the study. No significant increases in deaths resulted from rotenone exposure. Control, low dose and high dose groups experienced 23, 16 and 30 percent mortalities respectively, within the 18-month study period. No substantial difference in mortalities were experienced between the 2 sexes.

There were numerous mammary gland neoplasms observed both macroscopically and microscopically in animals from the control group and both treatment groups. Individual (Table 2) and group (Table 3) data are presented on the following pages. These were for the most part fibroadenomas and they occurred with similar frequency among control and treatment groups. In addition to the fibroadenomas, 2 adenomas occurred in females given 3.0 mg/kg and 3 in females given 1.7 mg/kg, the latter occurred in conjunction with fibroadenomas. Mammary carcinoma was present in 1 female given 3.0 mg/kg. Several fibroadenomas were also present in males from the control and 1.7 mg/kg groups. Fibroadenomas occurred in control rats with a frequency equal to or greater than that of treated groups, and the incidence of all female animals bearing mammary neoplasms was 53 percent, 52 percent, and 43 percent for the control, low and high dosage groups respectively (Table 3). The highest incidence of mammary neoplasms in male rats occurred in the control group. Other neoplasms which occurred in rats from this study are listed in Table 3. Two lymphosarcomas occurred in females given 3.0 mg/kg; all other neoplasms occurred in only 1 animal from any given dosage group with the exception of chromophobe adenomas of the pituitary gland and adrenal cortical adenomas which occurred with similar frequency among control and treatment groups.

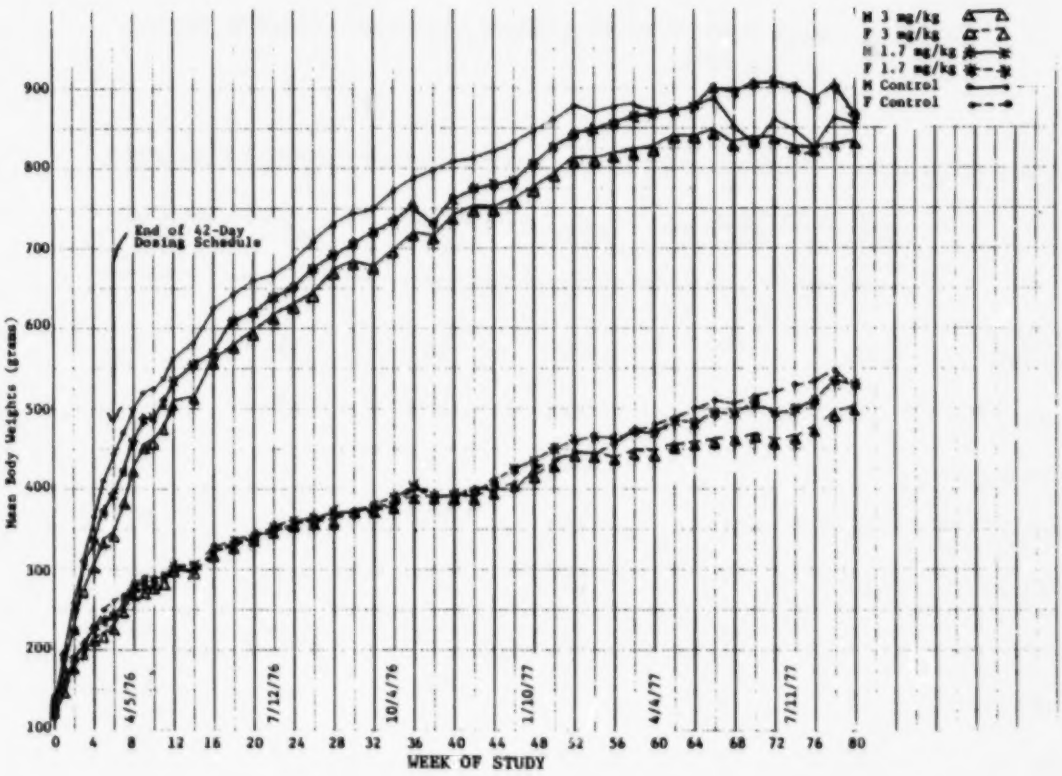

FIGURE 3. RAT 18-MONTH MEAN BODY WEIGHTS--ROTENONE (INTRAPERITONEAL) CARCINOGENICITY STUDY

TABLE 1. RATS SURVIVING FOLLOWING ROTENONE INTRAPERITONEAL INJECTIONS

	3.0 mg/kg		1.7 mg/kg		0	
	Male	Female	Male	Female	Male	Female
Initiated (2/76)	25	25	25	25	15	15
January 1,1977	21	21	24	25	15	15
February 1	21	21	24	24	15	15
March 1	21	21	24	24	14	14
April 1	20	21	24	23	12	14
May 1	18	20	24	23	12	13
June 1	18	19	23	23	12	13
July 1	17	19	23	23	11	12
August (Until Necropsy)	17	18	22	20	11	12

TABLE 2. NEOPLASTIC AND HYPERPLASTIC LESIONS BY DOSE GROUP, SEX[a], AND ANIMAL NUMBER (INTRAPERITONEAL STUDY)

Mammary Gland, Fibroadenoma

Control - 1129, 1117, 1116, 1112, 1111, 1110, 1109, 1108, 1107, 1104, 1102

1.7 - 1086, 1075, 1069, 1068, 1067, 1066, 1065, 1064, 1062, 1061, 1059, 1057, 1054, 1052

3.0 - 1021, 1003, 1019, 1017, 1016, 1014, 1002

Mammary Gland, Adenoma

Control - 1108

1.7 - 1075, 1065, 1054

3.0 - 1020

Mammary Gland, Hyperplasia

Control - None

1.7 - 1070, 1068

3.0 - None

Mammary Gland, Carcinoma

Control - None

1.7 - None

3.0 - 1016

Pituitary, Chromophobe Adenoma

Control - 1105, 1111

1.7 - 1054, 1055, 1087

3.0 - 1005, 1014, 1039

Pituitary, Chromophobe Hyperplasia

Control - 1101, 1102, 1113

1.7 - 1059, 1067, 1076, 1084, 1093, 1099

3.0 - 1033, 1036, 1004

(a) Males - Underlined.

TABLE 2. (Continued)

Adrenal, Cortical Adenoma

Control - 1101, 1102, 1103, 1105

1.7 - 1052, 1058, 1062, 1068, 1074

3.0 - 1003, 1021

Skin Keratoacanthoma

Control - 1122

1.7 - None

3.0 - None

Skin, Squamous Cell Carcinoma

Control - None

1.7 - 1091

3.0 - None

Skin, Pseudoepitheliomatous Hyperplasia

Control - None

1.7 - 1066

3.0 - None

Skin, Fibroma

Control - None

1.7 - 1082

3.0 - None

Skin, Fibrosarcoma

Control - None

1.7 - 1091

3.0 - None

TABLE 2. (Continued)

Skin, Sebaceous Adenoma	
Control	None
1.7	1084
3.0	None
Bone, Osteosarcoma	
Control	1119
1.7	None
3.0	None
Multiple Tissues, Lymphosarcoma	
Control	None
1.7	None
3.0	1024, 1002
Kidney, Pelvis, Hyperplasia	
Control	None
1.7	None
3.0	1009
Bladder, Transitional Cell Papilloma	
Control	None
1.7	1099
3.0	None
Testicle, Interstitial Cell Tumor	
Control	None
1.7	1078
3.0	None

TABLE 2. (Continued)

Uterus, Adenocarcinoma

Control - None

1.7 - None

3.0 - 1002

Liver, Hepatocellular Carcinoma

Control - None

1.7 - 1089

3.0 - 1040

Liver, Focus of Cellular Alteration

Control - None

1.7 - 1065

3.0 - None

Liver, Biliary Hyperplasia

Control - 1101, 1115

1.7 - 1071, 1074, 1077

3.0 - None

Pancreas, Islet Hyperplasia

Control - None

1.7 - 1095

3.0 - 1012

Pancreas, Ductular Hyperplasia

Control - 1103

1.7 - 1065, 1076

3.0 - None

TABLE 2. (Continued)

Pancreas, Islet Adenoma	
Control	None
1.7	1077, 1090
3.0	None
Stomach, Pseudoepithelial Hyperplasia	
Control	1109
1.7	1067
3.0	None
Salivary Gland, Hyperplasia	
Control	1107
1.7	1090
3.0	None
Lymph Node, Lymphoplasmatic Hyperplasia	
Control	1118, 1123, 1126
1.7	None
3.0	1001, 1026, 1032
Thyroid, Adenoma	
Control	1120
1.7	1088
3.0	None

TABLE 3. INCIDENCE OF NEOPLASTIC/HYPERPLASTIC LESIONS BY SEX AND DOSAGE GROUP (INTRAPERITONEAL ADMINISTRATION)

Organ and Lesion	Group					
	3mg/kg IP		1.7 mg/kg IP		Control	
	Male (n=23)	Female (n=21)	Male (n=24)	Female (n=25)	Male (n=14)	Female (n=15)
Kidney						
Hyperplasia, pelvic epithelium	0	1	0	0	0	0
Bladder						
Transitional cell papilloma	0	0	1	0	0	0
Thyroid						
Adenoma	0	0	1	0	1	0
Pituitary						
Chromophobe hyperplasia	2	1	4	2	0	3
Chromophobe adenoma	1	2	1	2	0	2
Adrenal						
Cortical adenoma	0	2	0	5	0	4
Spleen						
Extreme hematopoietic hyperplasia	0	1	0	1	0	1
Lymph node						
Lymphoplasmatic hyperplasia	2	1	0	0	3	0
Salivary gland						
Ductular hyperplasia	0	0	1	0	0	1
Stomach						
Pseudoepitheliomatous hyperplasia of squamous epithelium	0	0	0	1	0	1
Pancreas						
Islet hyperplasia	0	1	1	0	0	0
Islet adenoma	0	0	2	0	0	0
Ductular hyperplasia	0	0	1	1	0	1
Liver						
Hepatocellular carcinoma	1	0	1	0	0	0
Focus of cellular alteration	0	0	0	1	0	0
Biliary hyperplasia	0	0	1	2	0	2
Uterus						
Adenocarcinoma with metastasis	-	1	-	0	-	0

TABLE 3. (Continued)

Organ and Lesion	Group					
	3mg/kg IP		1.7 mg/kg IP		Control	
	Male (n=23)	Female (n=21)	Male (n=24)	Female (n=25)	Male (n=14)	Female (n=15)
Testicle						
Interstitial cell tumor	0	-	1	-	0	-
Skin						
Keratoacanthoma	0	0	0	0	1	0
Polyp	0	1	0	0	0	0
Squamous cell carcinoma	0	0	1	0	0	0
Pseudoepitheliomatous hyperplasia	0	0	0	1	0	0
Fibroma	0	0	1	0	0	0
Fibrosarcoma	0	0	1	0	0	0
Sebaceous adenoma	0	0	1	0	0	0
Mammary gland						
Fibroadenoma	0	7	1	13	3	8
Glandular hyperplasia	0	0	0	2	0	0
Adenoma	0	1	0	3	0	1
Carcinoma	0	1	0	0	0	0
Bone (rib)						
Osteosarcoma	0	0	0	0	1	0
Lymph node, spleen, liver, ovary						
Lymphosarcoma	0	2	0	0	0	0

The only non-neoplastic lesions which occurred with substantially greater frequency in rotenone-treated animals as compared to controls included myocardial fibrosis and/or lymphoreticular myocarditis in both the 1.7 and 3.0 mg/kg groups and cystic ductular dilatations in mammary glands of females given 3.0 mg/kg (Table 4).

Fourteen-Month Oral Carcinogenesis Study

A study was performed to examine the potential carcinogenicity of rotenone in a second strain of rats. This study employed oral gavage as the route of administration, again in an attempt to duplicate the studies of Gosalvez and Merchan.

Methods

One hundred and fifty Wistar rats were obtained from Charles River Company, 75 of each sex. The rat weights on the first day of dosing ranged from 75 to 145 grams for females, and from 81 to 156 grams for males. Animals were caged in pairs.

Rotenone was administered by oral gavage using a stainless steel feeding needle. The rotenone suspension was prepared as described in the 18-month study methods section. The rotenone in corn oil was given in 0.25 ml volumes daily for 42 consecutive days. Doses of 0, 1.7 or 3.0 mg rotenone per kilogram body weight were administered to groups of 25 males and 25 females. Following the 42-day administration period, the rats were observed for 12 months at which time the rats were necropsied.

Observations

The data in Figure 4 depict the body weights of the rats during the 14-month study. No appreciable differences are seen in body weights between the different groups throughout the study. Although this study was not as lengthy, nor did it use the same route of administration as the previous one described in this report, the Wistar strain appears to display lower sensitivity to rotenone administration as measured by body weights.

Survival data are presented in Table 5. Again, no significant number of deaths can be attributed to rotenone treatment in this study. Because of this

shorter observation period for this study, it is difficult to make comparisons on the lethality of rotenone in Wistar and Sprague-Dawley rats.

Neoplasms were observed in mammary glands of 3 female rats from this study, as indicated in Tables 6 and 7. Multiple adenomas (2) were present in 2 animals, one from the control group and one from the 1.7 mg/kg dosage group. A small early carcinoma and an adenocarcinoma were present in 2 different mammary glands from one animal in the 1.7 mg/kg dosage group. There were other small masses observed grossly in which mammary cysts, ductal or glandular ectasias or mild hyperplasias were observed microscopically. Ductal or glandular ectasias and cysts were slightly more prevalent in females from the 1.7 or 3.0 mg/kg dosage groups as compared to the control group.

Adrenal cortical adenomas occurred in slightly greater numbers in both the 1.7 and 3.0 mg/kg dosage groups as compared to the controls. These occurred in greater numbers in the females and occurred with similar frequency among females from both the high and low dosage levels.

Fibrosarcomas occurred in subcutaneous sites in 3 males from the 3.0 mg/kg dosage group and one fibroma was observed in a male rat from the 1.7 mg/kg dosage groups. Neither fibromas nor fibrosarcomas were observed in control groups in this study.

Bile duct hyperplasias were observed in 3 females and one male from the high dose group and one male from the control group. These were extremely mild changes and were not considered significant.

All other neoplastic or hyperplastic lesions occurred with similar or greater frequency in the control groups as compared to treated groups.

Other non-neoplastic changes (Table 8) generally occurred with similar frequency among control and treated groups. Chronic renal disease consisting of glomerular scleroses, thickening of tubular basement membranes with associated renal tubular epithelial regenerative changes, and in some instances chronic interstitial inflammatory changes (some or all of these changes) occurred in high percentages of male rats from all dosage groups and to a lesser extent in females. Likewise, respiratory disease was common in many animals: peribronchial and peribronchiolar lymphoid nodules were present in essentially all animals and were not listed in the diagnoses unless associated with other changes. Subacute enteritis, hepatic congestion, and lymphadenitis of mesenteric and mandibular lymph nodes occurred with slightly greater frequency in the 3 mg/kg dosage group than in controls; however, these variations were considered to be relatively insignificant.

TABLE 4. INCIDENCE OF NON-NEOPLASTIC LESIONS BY SEX AND DOSAGE GROUP (INTRAPERITONEAL ADMINISTRATION)

Organ and Lesion	Group					
	3mg/kg IP		1.7 mg/kg IP		Control	
	Male (n=23)	Female (n=21)	Male (n=24)	Female (n=25)	Male (n=14)	Female (n=15)
Lung						
Pneumonia	2	0	2	0	0	0
Bronchiectasis	0	0	1	0	0	0
Thrombosis	0	0	0	0	1	0
Heart						
Myocardial fibrosis, lymphoreticular myocarditis	11	4	22	8	4	0
Vessels						
Pyogranulomatous vasculitis	0	0	1	0	0	0
Kidney						
Nephritis (all developmental stages)	16	2	20	4	12	6
Bladder						
Cystitis	0	2	0	0	0	0
Stomach						
Granulomatous gastritis	0	0	0	1	0	0
Liver						
Hepatic necrosis	0	0	0	1	0	2
Vacuolar degeneration	0	0	0	2	0	1
Ovary						
Follicular cyst	-	2	-	0	-	1
Uterus						
Endometritis	-	2	-	0	-	0
Cystic glandular dilatation/hydrometra	-	1	-	1	-	1
Prostate						
Prostatitis	0	-	1	-	0	-
Muscle						
Myositis	0	0	1	1	0	0
Atrophy	0	0	1	0	0	0
Skin						
Dermatitis (all types)	3	0	2	1	4	0
Epidermoid cyst	2	0	1	0	0	0
Dilated hair follicles	1	0	0	0	0	0

TABLE 4. (Continued)

Organ and Lesion	Group					
	3mg/kg IP		1.7 mg/kg IP		Control	
	Male (n=23)	Female (n=21)	Male (n=24)	Female (n=25)	Male (n=14)	Female (n=15)
Subcutis						
Granulomatous steatitis	0	0	1	2	0	0
Fat necrosis (encapsulated, lipoma?)	0	0	0	1	0	2
Mammary gland						
Cystic ductular dilatations	1	3	1	11	0	6
Eye						
Retinal atrophy	0	0	1	0	0	0

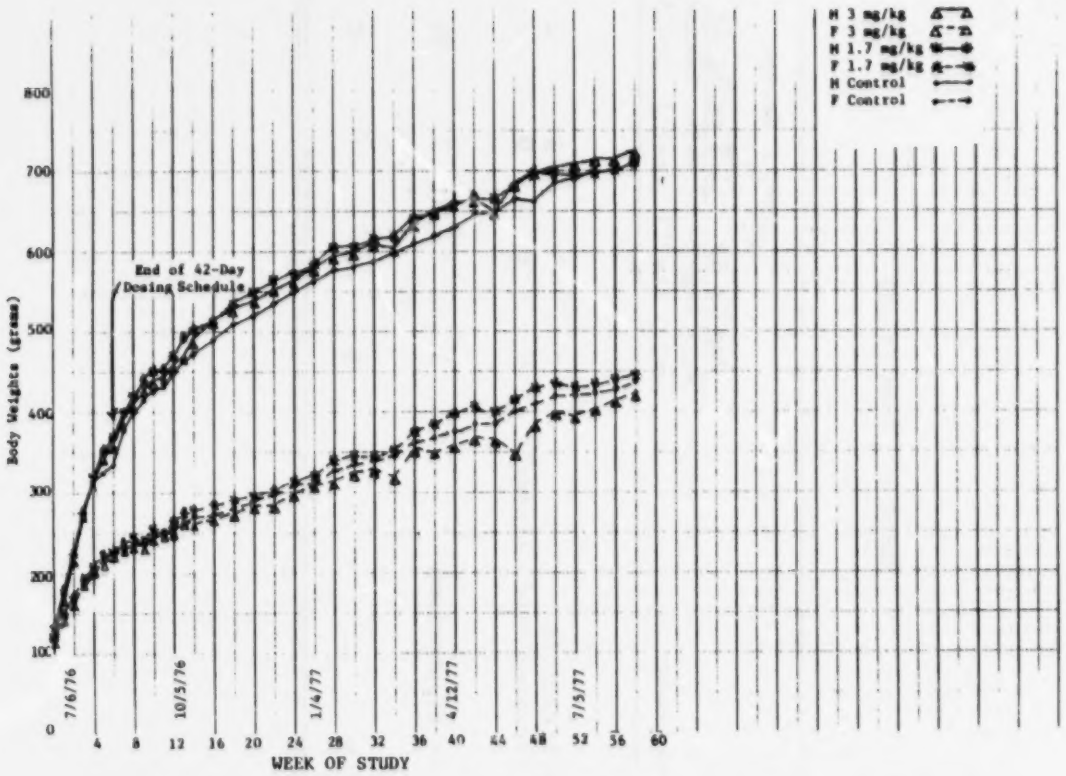

FIGURE 4. RAT 14-MONTH MEAN BODY WEIGHTS--ROTENONE (ORAL FEEDING) CARCINOGENICITY STUDY

TABLE 5. RATS SURVIVING FOLLOWING ROTENONE ORAL GAVAGE

	3.0 mg/kg		1.7 mg/kg		0	
	Male	Female	Male	Female	Male	Female
Initiated (6/76)	25	25	25	25	25	25
January 1,1977	25	24	25	24	25	25
February 1	25	24	25	24	25	25
March 1	25	24	25	24	25	25
April 1	24	24	25	24	25	25
May 1	24	24	25	24	25	25
June 1	23	24	25	24	25	25
July 1	23	24	24	24	25	25
August (Until Necropsy)	23	24	24	24	25	25

TABLE 6. NEOPLASTIC AND HYPERPLASTIC CHANGES BY DOSE GROUP, SEX[a], AND ANIMAL NUMBER (ORAL STUDY)

Adrenal Cortical Adenoma

Control - 2260, 2261, 2267, 2296

1.7 - 2203, 2204, 2205, 2211, 2212, 2223, 2224, 2238

3.0 - 2153, 2154, 2157, 2162, 2167, 2171, 2176, 2184, 2194

Adrenal Cortical Hyperplasia

Control - 2253, 2254, 2261, 2262, 2291, 2279, 2282, 2283, 2285, 2287, 2292, 2293, 2295, 2296, 2299, 2300

1.7 - 2205, 2206, 2208, 2214, 2220, 2232, 2237, 2238, 2243, 2247

3.0 - 2154, 2157, 2166, 2169, 2185, 2188, 2193, 2197

Adrenal Cortical Carcinoma

1.7 - 2212

Pituitary, Chromophobe Adenoma

Control - 2262, 2265, 2270, 2271

1.7 - 2202, 2205, 2215, 2225

3.0 - 2158, 2159, 2163, 2170, 2184, 2195, 2197

Pituitary Chromophobe Hyperplasia

Control - 2267, 2286, 2290, 2255, 2256, 2281

1.7 - 2214, 2210, 2216, 2223, 2224

3.0 - 2153, 2155, 2165, 2166, 2168, 2173, 2192

Pituitary Focus of Cellular Alteration

Control - 2264, 2256

1.7 - 2213, 2219

3.0 - 2161

Pituitary Adenoma, Pars Intermedia

1.7 - 2234

(a) Males - Underlined.

TABLE 6. (Continued)

Mammary Gland Ductal or Glandular Ectasia

Control - 2256

1.7 - 2202, 2204, 2211, 2213

3.0 - 2153, 2161, 2163, 2167, 2169, 2171

Mammary Gland Cyst

Control - 2258, 2262, 2268, 2271

1.7 - 2210, 2214, 2217

3.0 - 2151, 2155, 2157, 2169, 2173, 2174

Mammary Gland Adenoma

Control - 2255

1.7 - 2223

Mammary Gland Adenocarcinoma and Carcinoma

1.7 - 2215

Mammary Gland Hyperplasia

1.7 - 2223

3.0 - 2156, 2175

Skin - Fibroma

1.7 - 2245

Skin Fibrosarcoma

3.0 - 2177, 2183, 2188

Lymphosarcoma

Control - 2270, 2279

Liver, Neoplastic Nodule

Control - 2291

3.0 - 2166

Liver, Focus of Cellular Alteration

Control - 2292

3.0 - 2198

Thyroid Gland Follicular Adenocarcinoma

3.0 - 2166

TABLE 6. (Continued)

Thyroid Gland Follicular Hyperplasia

Control - 2282, 2284

3.0 - 2197

Thyroid Gland Medullary Carcinoma

Control - 2286

Liver, Bile Duct Hyperplasia

Control - 2300

3.0 - 2190, 2153, 2155, 2171

Diaphragm, Carcinoma of Undetermined Origin

Control - 2300

Skin Trichoepithelioma

3.0 - 2186

TABLE 7. INCIDENCE OF NEOPLASTIC AND OTHER GROWTH CHANGES INCLUDING MAMMARY GLAND CYSTS AND ECTASIAS BY SEX AND DOSAGE GROUP(ORAL ADMINISTRATION)

(Number in Parentheses Indicate Number in Group)

Diagnoses	Control		1.7 mg/kg Dosage Group		3 mg/kg Dosage Group	
	Female (25)	Male (25)	Female (24)	Male (25)	Female (24)	Male (25)
Adrenal Gland						
Cortical Adenoma	3	1	7	1	6	3
Cortical Carcinoma			1			
Cortical Hyperplasia	4	12	5	5	4	4
Pituitary Gland						
Chromophobe Adenoma	4		4		4	3
Chromophobe Hyperplasia	3	3	5		6	1
Focus of Cellular Alteration	2		2		1	
Adenoma, Pars Intermedia				1		
Thyroid Gland						
Follicular Adenocarcinoma					1	
Follicular Hyperplasia		2				1
Medullary Carcinoma		1				
Mammary Gland						
Cysts	4		3		6	
Adenoma	1		1			
Adenocarcinoma[a]			1			
Carcinoma[a]			1			
Ductal or Glandular Ectasia	1		4		6	
Hyperplasia			1		2	

(a) These neoplasms occurred in the same animal.

TABLE 7. (Continued)

Diagnoses	Control		1.7 mg/kg Dosage Group		3 mg/kg Dosage Group	
	Female (25)	Male (25)	Female (24)	Male (25)	Female (24)	Male (25)
Skin and Soft Tissue						
Fibroma				1		
Trichoepithelioma						1
Fibrosarcoma						3
Mesenteric Lymph Node						
Lymphosarcoma, focal	1					
Multiple Organs						
Lymphosarcoma		1				
Liver						
Neoplastic Nodule		1			1	
Focus of Cellular Alteration		1				1
Bile Duct Hyperplasia		1			3	1
Diaphragm						
Carcinoma, metastatic, (origin unknown)		1				

TABLE 8. INCIDENCE OF NON-NEOPLASTIC LESIONS BY SEX AND DOSAGE GROUP (ORAL ADMINISTRATION)

(Numbers in Parentheses Indicate Number in Group)

Diagnosis	Control		1.7 mg/kg Dosage Group		3 mg/kg Dosage Group	
	Female (25)	Male (25)	Female (24)	Male (25)	Female (24)	Male (25)
Heart						
Myocardial degeneration and/or necrosis	1			1	2	2
Myocardial fibroplasia	1					
Myocarditis acute or subacute	1	2	3	3	3	
Coronary artery, dystrophic mineralization			1			1
Papillary muscle, ectopic bone						2
Pericardial fat, necrosis and granulomatous inflammation with crystalline deposition	1					
Kidney						
Chronic renal disease[a]	5	19	6	22	5	18
Nephritis, acute						1
Cortex, medulla or pelvis, mineralization	4		9	1	2	
Medulla, granulomatous inflammation					3	
Hydronephrosis	1				1	
Congestion	5	1		1		
Pyelitis, suppurative			2			

(a) See text for definition of chronic renal disease.

TABLE 8. (Continued)

Diagnosis	Control		1.7 mg/kg Dosage Group		3 mg/kg Dosage Group	
	Female (25)	Male (25)	Female (24)	Male (25)	Female (24)	Male (25)
Kidney (continued)						
Nephritis, chronic active with papillary necrosis and abscessation		1				
Dilatation of Bowman's capsule			1			
Focal subcapsular cyst				2		
Cortical or pelvic lymphocytic infiltrates		2	1	1		
Liver						
Bile duct hyperplasia		1			3	2
Congestion		1	1		3	6
Hepatocyte degeneration			2	1		
Centrilobular necrosis				2		1
Focus of cellular alteration		1				1
Hepatitis, subacute			4	2		1
Extramedullary hematopoiesis					3	
Hepatocyte vacuolation	1	1	1	5		
Lung						
Congestion	2	3	3	3		
Granulomatous inflammation					1	2
Edema						1
Interstitial pneumonia	8	9	15	10	11	8

TABLE 8. (Continued)

Diagnosis	Control		1.7 mg/kg Dosage Group		3 mg/kg Dosage Group	
	Female (25)	Male (25)	Female (24)	Male (25)	Female (24)	Male (25)
Lung (continued)						
Hemorrhage		1				
Atelectasis		1				
Emphysema		1				
Developmental anomaly		1				
Alveolar macrophage accumulations	1					
Prostate Gland						
Prostatitis, suppurative, focal				1		
Prostatitis, subacute				1		2
Prostatitis, chronic, active, with necrosis				1		
Stomach						
Fundic mucosa, mineralization						1
Submucosa, edema						1
Submucosal cyst	1					
Gastritis, chronic, eosinophilic, with fibrosis		1				
Intestine						
Enteritis, subacute					4	3
Colon, parasitosis	1	2				
Jejunum, congestion			1			

TABLE 8. (Continued)

Diagnosis	Control		1.7 mg/kg Dosage Group		3 mg/kg Dosage Group	
	Female (25)	Male (25)	Female (24)	Male (25)	Female (24)	Male (25)
Lymph Nodes						
Mandibular lymph node, hemorrhage, hemosiderin congestion and/or lymphadenitis	4	3	2	6	10	4
Mandibular lymph node, fibroplasia				1		
Mesenteric or Mandibular lymph node, sinusoidal dilation				3		
Mesenteric lymph node, hemorrhage, hemosiderin, congestion, and/or lymphadenitis			1	1	1	6
Pancreatic lymph node, hemorrhage and hemosiderin			1			
Bronchial lymph node, ectopic tissue of uncertain origin				1		
Pituitary Gland						
Hemosiderin deposition	2	1				
Pars distalis chromophobe hyperplasia	2	2	1			
Pars nervosa, eosinophilic crystalline deposition	1					
Neurohypophyseal cleft, protein deposition				1		
Urinary Bladder						
Cystitis	1				1	1

TABLE 8. (Continued)

Diagnosis	Control		1.7 mg/kg Dosage Group		3 mg/kg Dosage Group	
	Female (25)	Male (25)	Female (24)	Male (25)	Female (24)	Male (25)
Pancreas						
Acinar cell atrophy	1		2			3
Focal ductal ectasia					1	
Fibrosis		1				
Pancreatic islets, fibrosis		5		4		
Pancreas or pancreatic islets, lymphocytic infiltrates	1	1		2		
Hemosiderin deposition		2				
Epididymis						
Lymphocytic infiltrate				1		
Testicle						
Artery mineralization		1				
Degeneration, fibrosis and/or atrophy		1		1		3
Ovary						
Follicular cysts	2					
Multilocular cysts					1	
Paraovarian cyst			1			
Thymus						
Branchial arch cysts					1	
Skin						
Subcutis, necrotizing phlebitis						1
Mammary gland, dermatitis, nonsuppurative, mild			1			

TABLE 8. (Continued)

Diagnosis	Control		1.7 mg/kg Dosage Group		3 mg/kg Dosage Group	
	Female (25)	Male (25)	Female (24)	Male (25)	Female (24)	Male (25)
Uterus (continued)						
Hemosiderin deposition	1					
Endometrium, lymphocytic infiltrate	1					
Endometrial glands, epithelial, hyperplasia			1			
Pulmonary artery						
Medial hypertrophy	1					
Mammary Gland						
Ductal or glandular ectasia	1		4		5	
Cysts	4		3		6	
Mastitis, granulomatous	1					
Hyperplasia			1		1	
Mastitis, chronic				1		
Parathyroid Gland						
Fibrosis	1					
Mandibular Salivary Gland						
Hyperplasia with cytomegaly		1				
Atrophy			1			
Degeneration, focal			1			
Hemosiderin deposition		1				

TABLE 8. (Continued)

Diagnosis	Control		1.7 mg/kg Dosage Group		3 mg/kg Dosage Group	
	Female (25)	Male (25)	Female (24)	Male (25)	Female (24)	Male (25)
Adrenal Gland						
Cortex, cytoplasmic vacuolation	3	1	1			
Cortical hyperplasia	4	12	5	5	4	4
Cortex, vascular ectasia	7		6		13	
Cortex, focus of cellular alteration	1					
Cortex, congestion	3	1	3	1		
Cortex, lymphocytic infiltrate	1					
Medulla, sinusoidal ectasia						2
Capsular fibrosis	1					
Thyroid Gland						
Parafollicular cell hyperplasia						3
Follicular hyperplasia		3				1
Cyst	2					
Eye						
Corneal vascularization and degeneration of Bowman's capsule					2	
Spleen						
Siderotic nodule						1
Trachea						
Submucosa, inflammatory infiltrate						1
Uterus						
Endometrial gland dilatation	2					

TABLE 8. (Continued)

Diagnosis	Control		1.7 mg/kg Dosage Group		3 mg/kg Dosage Group	
	Female (25)	Male (25)	Female (24)	Male (25)	Female (24)	Male (25)
Meninges						
Cerebellum, fibrosis				1		
Brain						
Encephalitis, nonsuppurative, multifocal				1		
Cerebrum, thromboembolic meningitis and encephalitis						1
Subependymal hemorrhage	1					
Sciatic Nerve						
Mineralization		1		1		
Femur						
Marrow cavity, fibrosis		1		5		

DISCUSSION

There was a striking difference between the incidence of mammary neoplasia among rats in the groups treated orally as compared to those which were exposed by intraperitoneal administration (Table 9). The incidence of mammary fibroadenomas in the intraperitoneal treatment group was as high in the control animals as in those given 1.7 mg/kg, and higher than the group given 3.0 mg/kg. The incidence of animals from the intraperitoneal study with mammary neoplasms was similar for rats in the 1.7 mg/kg and control groups since the three adenomas occurred in animals which also had fibroadenomas. The lowest incidence was recorded in those rats given 3.0 mg/kg. We interpret these data as showing no evidence that rotenone enhanced or induced mammary neoplasia in animals from the intraperitoneal study. Likewise, there was no evidence of enhanced induction of mammary neoplasia in animals from the oral treatment study.

The significantly higher incidence of mammary neoplasia in animals from intraperitoneal as compared to the oral treatment group reflects the difference in incidence of spontaneous mammary neoplasms in Wistar and Sprague-Dawley rats. The large numbers of spontaneous fibroadenomas commonly present in Sprague-Dawley rats was evident in this study and was in sharp contrast to the absence of this tumor type in the Wistar rats.

The absence of any evidence of increased tumor incidence in rotenone-treated animals from either the oral or intraperitoneal study is significantly different from results reported by Gosalvez and Merchan who reported an incidence of mammary tumors ranging from 60-100 percent which developed 6-11 months following intraperitoneal injections of 1.7 mg/kg of rotenone in 0.1 ml of sunflower oil for 42 days. The reason for the variation in test results is not known.

The significance of three fibrosarcomas and one fibroma which occurred in male rats from the 3.0 and 1.7 mg/kg dosage groups in the oral study is not clear. One fibroma and one fibrosarcoma also occurred in male rats given 1.7 mg/kg in the intraperitoneal study. Similar neoplasms were not present in control groups from either study. This is interpreted as suspicious but inconclusive evidence that the fibromas and fibrosarcomas were induced by the test compound.

TABLE 9. COMPARATIVE INCIDENCE OF MAMMARY GLAND NEOPLASIA IN RATS GIVEN ROTENONE BY ORAL AND INTRAPERITONEAL ROUTES

Route	Type of Neoplasm	No.	Treatment Level (No. in Group)	Sex	Incidence (%)
Oral	Adenoma	1	Control (25)	F	4.0%
Oral	Adenoma	1	1.7 mg/kg (24)	F	4.2%
Oral[a]	Carcinoma	1	1.7 mg/kg (24)	F	4.2%
Oral[a]	Adenocarcinoma	1	1.7 mg/kg (24)	F	4.2%
I.P.	Fibroadenoma	8	Control (15)	F	53.3%
I.P.	"	3	Control (14)	M	21.4%
I.P.	"	13	1.7 mg/kg (25)	F	52.0%
I.P.	"	1	1.7 mg/kg (24)	M	4.2%
I.P.	"	7	3.0 mg/kg (21)	F	33.3%
I.P.[b]	Adenoma	3	1.7 mg /kg (25)	F	12.0%
I.P.	"	1	3.0 mg/kg (21)	F	4.7%
I.P.	"	1	Control (15)	F	6.6%
I.P.	Carcinoma	1	3.0 mg/kg (21)	F	4.8%

(a) Occurred in same animal.

(b) All three adenomas in this group occurred in animals which also had fibroadenomas.

A greater incidence of adrenal cortical adenomas occurred in the treated groups when compared to control groups from the oral study. The significance of these differences is difficult to interpret in view of the small number of animals included in these groups and the relatively high incidence of these changes which were present in control groups.

CONCLUSIONS

1. There was no evidence that rotenone induced mammary neoplasia in animals from these studies.
2. The correlation between rotenone treatment and the fibrosarcomas and fibromas induced in both oral and intraperitoneal studies is inconclusive.
3. The significance of the increased numbers of adrenal cortical adenomas in animals from treated groups in the oral study is unclear.